

NATIONAL INSTITUTES OF HEALTH
FISCAL YEAR 2006

PLAN FOR HIV-RELATED RESEARCH

FY2006

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Dedicated to the memory of

Dr. John R. La Montagne
Deputy Director, National Institute of Allergy
and Infectious Diseases

An AIDS research pioneer and friend

January 1, 1943–November 2, 2004

OVERVIEW

Foreword

As the Director of the Office of AIDS Research (OAR), I am pleased to present the National Institutes of Health (NIH) Fiscal Year 2006 Plan for HIV-Related Research. Each year, we develop a comprehensive research plan through a unique collaborative process involving broad input from the community of government and nongovernment scientists and other experts from the United States and abroad. It is essential that the Plan be responsive to the changing nature of the epidemic, to emerging scientific opportunities, and to the needs of affected communities around the world. The input of these experts helps to ensure such responsiveness.

Many individuals—researchers from academia and industry; representatives of foundations and other nongovernmental organizations in the United States and abroad; community representatives; representatives of other governmental agencies; members of the OAR Advisory Council; and Directors of the NIH Institutes and their staffs—have given generously of their time to provide us with their expertise and thoughtful opinions in the development of this Plan. I thank each of them, for it is their thoughtful consideration and advice that makes this document a valuable tool for the OAR and the NIH.

Through this planning effort, we attempt to articulate a roadmap for the NIH research effort that both comprehensively defines the full range of activities needed to combat HIV and AIDS and identifies specific priorities for new or expanded funding. The Plan serves as the framework for the development and execution of the NIH AIDS budget and thus is an integral

component of the budgeting process, providing essential guidance for funding decisions.

The staff of the OAR and I sincerely believe that the fruits of the research efforts outlined within the Plan will help to control the pandemic, prevent new infections, and care for those infected and affected by HIV and AIDS around the world.

A handwritten signature in black ink, reading "Jack Whitescarver". The signature is fluid and cursive, with the first name "Jack" being more prominent and the last name "Whitescarver" following in a similar style.

Jack Whitescarver, Ph.D.
Director, OAR
August 2004

Legislative Mandate

The National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) provided that the Director of the Office of AIDS Research (OAR) “shall plan, coordinate and evaluate research and other activities conducted or supported” by the NIH. The Director of OAR “shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health” and “shall establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health...; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities...; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan.” The law further provides that “the Director of the OAR shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is supported and conducted by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social science research.”

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Introduction

THE GLOBAL HIV/AIDS PANDEMIC

A new United Nations report, “The Impact of AIDS,” presents a devastating picture of the global pandemic, highlighting its impact on families, agriculture and famine, business, health care, education, and national economic growth: “The HIV/AIDS epidemic has erased decades of progress in combating mortality and has seriously compromised the living conditions of current and future generations.”¹ The United Nations General Assembly’s Declaration of Commitment on HIV/AIDS states “...the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society—national, community, family, and individual.”²

| Group | People Newly Infected in 2003 | People Living with HIV/AIDS | AIDS Deaths in 2003 |
|--------------|-------------------------------|-----------------------------|---------------------|
| Adults | 4.2 Million | 38.6 Million | 2.5 Million |
| Women | 2.0 Million | 19.2 Million | 1.2 Million |
| Children | 700,000 | 2.5 Million | 500,000 |
| Total | 5.0 Million | 40.0 Million | 3.0 Million |

Source: UNAIDS

¹ “The Impact of AIDS” (Department of Economic and Social Affairs, United Nations, 2003).

² Ibid.

A Central Intelligence Agency (CIA) report stated, “By 2010, we estimate that five countries of strategic importance to the United States—Nigeria, Ethiopia, Russia, India, and China—collectively will have the largest number of HIV/AIDS cases on earth.”³ *Foreign Affairs* magazine stated: “The spread of HIV/AIDS through Eurasia, in short, will assuredly qualify as a humanitarian tragedy—but it will be much more than that. The pandemic there stands to affect, and alter, the economic potential—and by extension, the military power—of the region’s major states....Over the decades ahead, in other words, HIV/AIDS is set to be a factor in the very balance of power within Eurasia—and thus in the relationship between Eurasian states and the rest of the world.”⁴ Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean.

HIV has already infected more than 60 million people around the world, and AIDS has surpassed tuberculosis (TB) and malaria as the leading infectious cause of death worldwide.⁵ Another dimension to the epidemic in Africa was cited in the *New York Times*: “As a result of HIV, the worst-hit African countries have undergone a social breakdown that is now reaching a new level: African societies’ capacity to resist famine is fast eroding. Hunger and disease have begun reinforcing each other.”⁶

Curbing the transmission of HIV from infected mother to infant is an especially compelling challenge in resource-poor countries. The coexistence of other endemic diseases widely prevalent in developing countries, such as respiratory and gastrointestinal infections, complicates treatment and poses additional problems for medical personnel caring for HIV-infected individuals.

³ “Intelligence Community Assessment: The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China” (CIA, 2002).

⁴ “The Future of AIDS,” *Foreign Affairs*, November/December 2002.

⁵ “Report on the Global HIV/AIDS Epidemic: July 2002” (UNAIDS/WHO, Geneva, Switzerland, 2002).

⁶ A. de Waal, “What AIDS Means in a Famine,” *New York Times*, 11/19/02.

THE EPIDEMIC IN THE UNITED STATES

The HIV/AIDS epidemic in the United States continues to evolve. According to Centers for Disease Control and Prevention (CDC) statistics, the decline in death rates observed in the late 1990s, due largely to expanded use of new antiretroviral therapies (ART) that prevent progression of HIV infection to AIDS, has now leveled off, and AIDS incidence increased 2 percent in 2002 (over 2001). This means that the overall epidemic is continuing to expand.^{7 8 9} In addition, use of ART has now been associated with a series of side effects and long-term complications that may have a negative impact on mortality rates. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age.^{7 10} The appearance of multidrug-resistant strains of HIV presents an additional serious public health concern.^{11 12 13 14 15} These data forebode an epidemic of even greater magnitude in the coming years.

According to CDC reports, approximately one-quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV coinfection is found in 50 to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV.¹⁶

AIDS disproportionately affects African Americans and Hispanics. According to CDC figures through December 2001, approximately 64 percent of newly infected women are African American and 17 percent are Hispanic. Among newly infected men, approximately 43 percent are African American and 20 percent are Hispanic.¹⁷

⁷ CDC Year-End HIV/AIDS Surveillance Report for 2002 (CDC, 2003).

⁸ "Centers for Disease Control and Prevention HIV Prevention Strategic Plan Through 2005" (CDC, 2001).

⁹ "HIV/AIDS Update—A Glance at the HIV Epidemic" (CDC, 2001).

¹⁰ "U.S. HIV and AIDS Cases Reported through June 2000," *CDC HIV/AIDS Surveillance Report*, Vol. 12 (2000).

¹¹ N. Loder, *Nature* 407, 120 (2000).

¹² H. Salomon et al., *AIDS* 14, 17 (2000).

¹³ Y.K. Chow et al., *Nature* 361, 650 (1993).

¹⁴ M. Waldholz, "Drug Resistant HIV Becomes More Widespread," *Wall Street Journal*, 2/5/99.

¹⁵ "World Health Report on Infectious Diseases: Overcoming Antimicrobial Resistance" (WHO, Geneva, 2000).

¹⁶ "Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus" (CDC, 2002).

¹⁷ "U.S. HIV and AIDS Cases Reported through Dec. 2001," *CDC HIV/AIDS Surveillance Report*, Vol. 13 (2001)

THE NIH AIDS RESEARCH PROGRAM

To respond to this pandemic, the NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat and control HIV disease, and design interventions to prevent new infections from occurring. The NIH supports AIDS research both in NIH intramural laboratories and at academic and medical institutions in the United States and internationally. The Office of AIDS Research (OAR) is mandated by public law to plan and coordinate the AIDS research programs sponsored by all of the NIH Institutes and Centers (ICs).

The Role of the Institutes

Nearly every NIH component supports HIV/AIDS-related research activities, consistent with its individual mission. A list of NIH ICs is found at the back of this Plan. The ICs whose research programs are most heavily focused on HIV, AIDS, and their sequelae are the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), the National Center for Research Resources (NCRR), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Child Health and Human Development (NICHD). The Warren Grant Magnuson Clinical Center provides the infrastructure for intramural clinical studies sponsored by the ICs. A summary of HIV/AIDS funding by IC for fiscal years 2003–2005 is provided in Appendix A of this Plan Overview.

Office of AIDS Research

Mission: OAR, located within the Office of the Director (OD), was established in 1988 to coordinate the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program and to serve as the principal liaison with the U.S. Department of Health and Human Services (DHHS), other Federal agencies, and domestic and international governmental and nongovernmental organizations on behalf of NIH AIDS-related research. The NIH represents the largest and most significant public investment in AIDS research in the world. Our response to the epidemic requires a unique and complex multi-Institute, multidisciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH ICs. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently. This is recognized

in the unique role given OAR, relative to other OD Offices, in its authorizing legislation, the NIH Revitalization Act of 1993. That law establishes OAR as a model for trans-NIH coordination, vesting it with primary responsibility for overseeing all NIH AIDS-related research, and thus allowing the NIH to pursue a united research front against the global AIDS epidemic.

Evaluation: OAR has authority to evaluate NIH AIDS-related research programs. Several years ago, OAR completed a major evaluation of the entire NIH AIDS research program, utilizing the expertise of nongovernment scientists and AIDS community representatives. That review led to a number of significant changes in the overall direction of the AIDS research program, including bringing new focus to such areas as human immunology, vaccine research, and other areas of HIV prevention science. OAR continues to support periodic reviews of areas of AIDS research as well as specific programs across the Institutes.

Trans-NIH Coordination: OAR plays a crucial role in identifying scientific areas that require focused attention and facilitating multi-Institute activities to address those needs. This is a two-way process. In some cases these issues are raised within OAR and shared with the Institutes; in other cases, one or more Institute may ask OAR to bring other Institutes together to address an area of research or to cosponsor a specific grant, project, or initiative. OAR can foster these efforts through a number of mechanisms, such as designating funds and supplements to jump-start program areas; sponsoring workshops or conferences to highlight a particular research topic; sponsoring reviews or evaluations of research program areas to identify scientific opportunities, gaps, or needs; and establishing working groups or committees.

For example, a number of years ago OAR identified microbicides research as an area needing additional attention. Microbicides research has proved particularly challenging, as there is no definitive clinical evidence as yet establishing that a product applied topically in humans can prevent HIV transmission. To enhance and facilitate research in this area, OAR established a Trans-NIH Microbicides Working Group, comprised of program staff of relevant Institutes and Offices; cosponsored the first international conference on microbicides; spearheaded the development of the NIH Strategic Plan for Microbicides and a broader governmentwide plan; and provided supplemental funds to the Institutes to accelerate microbicide research.

OAR also has placed high priority on research to address the disproportionate impact of the epidemic on racial and ethnic minority communities in the United States. OAR is directing increased resources toward (1) new and innovative interventions that will have the greatest impact on these groups and (2) efforts to improve research infrastructure and training opportunities for minorities.

International AIDS Research: Another area of OAR leadership is in addressing the urgency of the global AIDS epidemic. OAR coordinates, monitors, and fosters plans for NIH involvement in international AIDS research and training activities. OAR established a broad initiative and strategic plan for global research on HIV/AIDS aimed at slowing the pandemic and reversing its devastating effects on individuals, communities, economies, and nations worldwide. The Global AIDS Research Initiative and Strategic Plan and the budget commitment that derives from it reaffirm the NIH's long-standing support for international AIDS research and will help to significantly expand our efforts to benefit resource- and infrastructure-poor nations.

Organization: An "AIDS Coordinator" is designated in each IC to serve as the point of contact with OAR. OAR is required by law to establish and support Coordinating Committees for each research discipline of AIDS research. These committees allow OAR to stay abreast of the scientific programs across the NIH, to foster collaboration and coordination, and to develop the annual NIH plan and budget. OAR senior staff chair these coordinating groups and work with the Institutes to facilitate research. The OAR Advisory Council provides expert advice to the Director of OAR and DHHS Secretary. Its members include nongovernment experts from a broad array of scientific disciplines as well as AIDS community representatives; representatives of Advisory Councils from the NIH Institutes with the largest AIDS research portfolios; and representatives from other Federal agencies conducting AIDS research, including the Department of Defense, the Department of Veterans Affairs, and the CDC, providing further opportunity for coordination and collaboration.

OVERVIEW OF THE PLAN

The Planning Process

OAR has established a unique and effective model for developing a consensus on scientific priorities for the annual comprehensive *NIH Plan for HIV-Related Research*. To develop the FY 2006 Plan, OAR sponsored a series of planning workshops to seek the input of non-NIH experts from academia, foundations, industry, and the AIDS-affected community. These experts participated with NIH scientific and program staff in Planning

Groups for Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science; Microbicides; HIV Prevention Research; Racial and Ethnic Minorities; Women and Girls; and International Research. A list of participants in the Planning Groups is found in their respective sections of the FY 2006 Plan. Participants in each Planning Group were asked to review and revise the objectives and strategies of the Plan, based on the state of the science, and to identify a set of priorities for their area. All groups were asked to address needs in Information Dissemination and Training, Infrastructure, and Capacity Building as related to their area. The resulting draft Plan was then provided to each IC Director and AIDS Coordinator for recommendations and comments. Finally, the Plan was reviewed by the Office of AIDS Research Advisory Council (OARAC). A list of current OARAC members is included in Appendix B. OAR continues to reassess the planning process and make refinements in order to better capture the broadest range of scientific expertise and community participation and to facilitate the identification of specific scientific priorities.

Structure of the Plan

The structure of the Plan is designed to comprehensively describe research activities that are needed to address HIV and AIDS, define specific research priorities, and reflect mutual reinforcement among the scientific and crosscutting areas. Each of these sections of the Plan includes (1) Scientific Issues and Priorities and (2) Objectives and Strategies.

Scientific Issues and Priorities: This section provides a scientific overview and specific priorities identified by the Planning Groups. These priorities narrowly define a few key areas deemed most worthy of new or expanded funding based on the current scientific knowledge, opportunities, and gaps. They will be used to guide the development of the FY 2006 AIDS budget and to adjust the FY 2005 AIDS budget as needed.

Objectives and Strategies: This section consists of a comprehensive list of Objectives, in priority order, that address the many needs and challenges within the field of HIV/AIDS research. Each Objective is followed by a set of Strategies that provide examples of approaches that might be taken to fulfill each Objective. To underscore the interrelationships among areas, strategies may be found under more than one Area of Emphasis.

Uses of the Plan

The Plan serves several important purposes:

- As the framework for developing the NIH AIDS research budget. A chart showing the relationship between the planning and budget process may be found in Appendix C.
- For determining the use of NIH AIDS-designated dollars and for tracking and monitoring those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allocated.
- As a document that provides information to the public, the scientific community, Congress, and the AIDS-affected communities about the NIH AIDS research agenda. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: <http://www.nih.gov/od/oar>.

Trans-NIH Comprehensive AIDS Research Budget: The law provides that OAR shall allocate all appropriated AIDS research funds to the Institutes. The Plan initiates the annual budget development and allocation process. Based on the priorities and objectives established in the Plan, the ICs submit their AIDS-related research budget requests to OAR, focusing on new or expanded program initiatives for each scientific area. OAR reviews the IC initiatives in relation to the Plan, to OAR priorities, and to other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The NIH Director and the OAR Director together determine the total amount allocated for AIDS research within the overall NIH budget, as required by law. Within that total, OAR allocates the AIDS research budget levels to each IC, based on the scientific priority of the proposed initiatives, at each step of the budget development process up to the time of the final congressional appropriation. This involves consulting regularly with the IC Directors and maintaining knowledge of the ongoing scientific research programs and planned initiatives supported by each IC. This process allows OAR to ensure that NIH AIDS-related research funds will be provided to the most compelling scientific opportunities, rather than distributed simply by a formula.

As congressionally mandated, OAR also prepares an annual “bypass” budget for submission directly to the President. This bypass is essentially a professional judgment budget, based solely on scientific need and opportunity, without regard to cost.

Major Themes of the Plan

The FY 2006 NIH AIDS research agenda continues the following overarching themes: HIV prevention research, including development of vaccines, microbicides, behavioral interventions, and strategies to prevent perinatal transmission; therapeutics research to develop simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated illnesses, malignancies, and other complications; international research, particularly to address the critical research and training needs in developing countries; and research targeting the disproportionate impact of the AIDS epidemic on racial and ethnic minority populations in the United States. All of these efforts require a strong foundation of basic science. The key priorities for each research area of the Plan and directions for future research are summarized below.

NATURAL HISTORY AND EPIDEMIOLOGY

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Sponsor domestic and international epidemiologic studies to characterize modes of transmission, including host characteristics (e.g., sexual behavior, substance use, use of blood products and other injections, effects of treatment, genetic variation) and viral characteristics (e.g., subtype, viral load, drug resistance, tropism), or continued risk behaviors in HIV-infected and uninfected populations of adults, adolescents, and children.**
- **Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics to establish databases that support analyses of host and viral characteristics. Use this approach as the basis for the use of integrated databases to:**
 - ▶ **Assess the impact of interventions on HIV-related outcomes through the use of operations research;**
 - ▶ **Evaluate treatment effectiveness at the individual and population levels; and**
 - ▶ **Increase the understanding of the pathogenesis of HIV infection and disease.**
- **Implement epidemiologic and simulation studies among HIV-infected individuals and appropriate controls to inform, monitor, and evaluate intervention strategies and to optimize surveillance in domestic and international settings.**
- **Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; markers of toxicity and comorbidity, and markers of recent infection for use in domestic and international settings; and HIV-related normative parameters for clinical and laboratory settings in resource-limited countries.**
- **Characterize the interactions between HIV, host genetics, and the major environmental factors that influence outcomes (viral transmission, response to therapy, comorbidities, and disease progression). This includes how viral genetic variability interacts with the host in the context of different routes of transmission, comorbidities, and host genetic variants or other determinants of the immune response.**

Natural history and epidemiologic research is needed to monitor epidemic trends, develop and evaluate prevention modalities, follow the changing clinical manifestations of HIV disease in different populations, and measure the effects of treatment regimens. The NIH will continue to support research to examine topics in HIV transmission, HIV/AIDS disease progression (including the occurrence of opportunistic infections [OIs]), malignancies, metabolic complications, neurological and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions. Domestically, as well as internationally, the populations affected by HIV/AIDS are also those most severely affected by the spreading epidemics of sexually transmitted diseases (STDs), TB, and other comorbidities, such as HCV. Researchers are studying the effects of viral, host, and other factors on transmission and disease progression. Since biological, pharmacological, psychological, and behavioral factors all potentially influence the impact of ART on HIV transmission, researchers are evaluating the specific contributions of these factors and their net impact on HIV transmission. Research also is focusing on determining the biological characteristics, sociocultural factors, and health services issues that contribute to the differential dynamics of HIV transmission and disease progression in men, women, and different racial/ethnic groups. Results from these studies will provide new directions and improvements in HIV/AIDS prevention and care.

The NIH will continue to emphasize the importance of epidemiologic studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the spectrum of HIV disease. The expansion of existing study populations in the United States will allow the identification of long-term effects of HIV therapy. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key cofactors that modify HIV disease. The NIH will foster basic and applied research to develop inexpensive virologic, immunologic, and genetic assays for use in domestic and developing country settings.

ETIOLOGY AND PATHOGENESIS

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection. Identify and validate cofactors for viral genes as new targets capitalizing on novel technologies including RNA interference and genomic screening.**
- **Elucidate the biologic determinants of HIV transmission between individuals, and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of virus transmission and dissemination.**
- **Understand the dynamic of virus-host interaction through the course of HIV infection.**
- **Investigate the mechanisms of persistence of HIV infection.**
- **Develop innovative technologies in human and nonhuman primate immunology to guide vaccine development and immune reconstitution efforts.**
- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of ART and the factors that underlie changes in the causes of morbidity and mortality in an era of increasingly effective therapies.**

Of paramount importance in our fight against HIV/AIDS is maintaining a strong commitment to basic research. Tremendous progress has been made in understanding the fundamental steps in the life cycle of HIV, the host-virus relationship, and the clinical manifestations associated with HIV infection and AIDS. Groundbreaking research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, the methodologies for diagnosis, and the monitoring for efficacy of antiviral therapies. In spite of these achievements, we still do not have a clear understanding of major aspects of viral interaction with the infected individual, the nature of the immune response to the virus, how the virus establishes infection and spreads throughout the body, and its mechanisms of pathogenesis. This basic knowledge is critical for our efforts to prevent and control HIV infection and disease progression. A substantial portion of NIH AIDS-related research will continue to be devoted to basic research.

Some of the outstanding questions within the area of etiology and pathogenesis research include: What role do the specific products of HIV (the viral genes and their protein products) play in the viral life cycle in

individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other systems that HIV affects? What host factors and cofactors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, OIs, neurological impairments, and metabolic abnormalities that characterize AIDS?

Research is focusing on the different mechanisms of viral persistence to understand the reasons for drug failure, to design rational approaches for virus eradication, and to better assess the impact of persistence on HIV transmission and its implications for HIV prevention. HIV can persist in a latent reservoir of resting memory CD4 T cells that is established very early after infection and by continuously replicating, albeit at very low levels, even in the presence of ART that can drive viral load below the limits of detection.

Understanding the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to designing rational immune reconstitution approaches in persons undergoing ART and identifying the characteristics of the immune response that are needed for a protective vaccine.

The basic science underlying HIV etiology and pathogenesis research is generally gender neutral. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. Studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. Transmission of HIV from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or after birth through breastfeeding. Many basic research questions associated with maternal-fetal transmission remain unclear and are actively under investigation.

AIDS is associated with a broad spectrum of cancers and tumors. As HIV causes immunosuppression and most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. Elucidation of the interactive factors involved in

the pathogenesis of AIDS-associated malignancies will possibly translate into the identification of new targets for prevention and treatment.

HIV infection results in the progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-infected individuals. OIs can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. The NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs.

THERAPEUTICS

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Advance the discovery and validation of new viral and cellular targets. Develop new therapeutic agents that: target drug-resistant virus; have activity in viral reservoirs and cellular compartments; and have improved pharmacologic and toxicologic properties.**
- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies. Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost. Identify immunologic correlates of effective viral suppression in the setting of clinical therapeutic intervention trials.**
- **Target affected populations, especially women, IDUs, children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.**
- **Develop safe, effective, feasible, and conveniently administered strategies to interrupt mother-to-child transmission (MTCT) of HIV with a focus on resource-limited settings and a special emphasis on breastfeeding.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of antiretrovirals (ARVs) to prevent HIV transmission in women during pregnancy, and in their offspring who were perinatally exposed. Evaluate the effects of short-course ARV prophylaxis regimens, including ART, used for prevention of MTCT in domestic and international settings, on development of drug resistance and the effects of drug resistance on efficacy of prophylaxis, and responses to future ART in women and infants who become infected despite prophylaxis, and develop interventions to prevent development of such resistance in women and infected infants.**
- **Evaluate interventions, including ARV and immunotherapeutic, in clinical trials to reduce horizontal transmission during both acute and chronic HIV infection, in domestic and international settings. Evaluate the risk of resistance on HIV acquisition and transmission during interventional studies designed to reduce horizontal transmission.**

- **Evaluate the effects of coinfection, especially with hepatitis B virus (HBV), HCV, TB, or malaria, on the management of HIV. Determine the bidirectional effects of coinfection and treatments on disease progression and drug interactions. Develop new agents for the treatment of HBV, HCV, TB, and malaria in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**
- **Develop and evaluate therapeutic approaches including vaccines that will improve and sustain immune function or prevent transmission of HIV infection. Identify and validate immunologic determinants to predict the efficacy of immune-based therapies.**
- **Expand international clinical research programs in countries with limited resources. Design and conduct clinical studies that are appropriate for diverse international settings. Design studies to improve and facilitate the delivery of therapeutic and prevention interventions for HIV disease. Encourage studies that integrate therapeutic regimens and prevention interventions. Evaluate the clinical and public health impact of ARV treatment. Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for coinfections/OIs, AIDS-related malignancies, and other cancers.**

Today, many HIV-infected people are living with the benefits resulting from NIH-supported research in this area. The development of combination regimens including protease inhibitors has extended the length and quality of life for many HIV-infected individuals in the United States and Western Europe. Unfortunately, however, ART has failed to eradicate HIV, and a growing proportion of patients receiving therapy experience treatment failure. Some patients find it difficult or impossible to comply with arduous treatment regimens, develop toxicities and side effects, or cannot afford their high cost. Others fail to obtain a satisfactory reduction in viral load even while adhering to treatment regimens. An increasing number of treatment failures are linked to the increasing emergence of drug-resistant HIV. In addition, metabolic complications, including insulin resistance, and body composition changes such as deforming deposits of abdominal adipose tissue, have emerged in individuals who have been on long-term ARV regimens. These side effects and complications appear to be increasing as HIV-infected patients continue on the drug regimens. More deaths occurring from liver failure, kidney disease, and cardiovascular complications are being observed in this patient population.

The need for simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated OIs, malignancies, and other complications continues to be a critical priority. This includes the discovery and development of the next generations of antiviral drugs directed against new cellular and viral targets. Clinical trials will help to better define when to begin and/or switch drugs within a regimen, as well as to identify regimens for treatment-experienced individuals who no longer respond to these anti-HIV drugs. Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to drug-drug interactions and adherence. Protease inhibitors, in particular, interact with each other and many other medications commonly used by HIV-infected individuals. Additional research is underway and planned with the goal of minimizing viral replication and delaying disease progression, drug resistance, and development of manifestations such as metabolic complications and body composition changes. Important studies are planned to evaluate delayed and long-term effects of these ARV drugs.

Studies are answering the following questions: When should ART be initiated? When should they be changed? How long can successful therapies maintain decreased viral loads, increased CD4 counts, and improved clinical outcomes? What is the basis for the emergence of drug resistance, and how can it be prevented? Can treatment strategies be developed for patients who no longer respond to current regimens? Can therapeutic approaches rebuild the immune system, so that disease progression is delayed? Can treatment strategies be developed to eliminate HIV, so that it is not transmitted from an infected individual to others?

Recent advances in therapeutics research underscore the importance of continued and further collaboration of Government- and industry-sponsored drug development research and clinical trials with the common goal of developing therapeutic regimens that slow disease progression, extend lifespans, and improve the quality of life for HIV-infected individuals.

VACCINES

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Maintain a strong NIH research portfolio to ensure a continuing vigorous program of basic and preclinical research for discovery, preclinical evaluation, and introduction of new vaccine candidates and immunization concepts. This remains a key overarching priority that needs to be balanced with the urgency to develop and test existing HIV vaccine candidates in domestic and international cohorts.**
- **Emphasize support for basic vaccine design research, particularly innovative research on immune responses to HIV envelope to address the issues related to improvement in the breadth of the immune response.**
- **Continue to support basic research on the identification of correlates of immune protection: study the development and maintenance of immune responses to HIV antigens, particularly at mucosal surfaces, and address issues related to improvement in the duration of potentially protective immune responses.**
- **Implement direct “head-to-head” and comparative studies to assess immune responses in both preclinical and clinical evaluation of HIV vaccine candidates. Appropriate reagents, assays, and animal models should be developed and the information and reagents shared widely to facilitate comparative vaccine studies. This includes development, identification, selection, and production of virus stocks for shared use in widely accepted animal NHP models. To ensure comparability, expanded assessments of cellular immunity and neutralizing antibodies in central laboratories using validated assays and broader access to specimens are encouraged for both academic and industrial investigators.**
- **Improve the linkage of vaccine design efforts with the clinical trial networks and cohorts being developed for clinical trials to better integrate the animal model data into human vaccine trial planning and to inform all stakeholders. Conduct appropriate preparative work in trial sites, particularly in international sites and minority communities, to provide critical viral and immunological information to inform vaccine trial design while helping to develop strong, sustainable research infrastructure.**

- **Develop and implement a defined plan with specific goals to educate high-risk populations and communities in the United States and international sites about HIV vaccines. In particular, continue to develop tools, devise outreach programs, and implement strategies to involve minority populations as well as international populations in HIV vaccine trials that will be testing products for efficacy.**

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. As a result of increased funding from the NIH in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued. Basic research in vaccine design and studies of immune responses in small animals and NHPs as well as vaccine product development are underway. Recent HIV vaccine research studies in animal models have provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional candidate vaccines into clinical testing. Although production of candidate vaccines for clinical study has proceeded slowly, at least 10 new candidate vaccines will enter Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide better immune responses, also will be tested in Phase I or II trials. The Dale and Betty Bumpers Vaccine Research Center recently launched the first Phase I clinical trial of a multiclade, multigene vaccine candidate.

The NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on candidate vaccine products. As promising candidates move further in the vaccine pipeline, expanded trials with populations at increased risk for HIV infection will become increasingly important. HIV/AIDS vaccine research requires trained health care, medical research, and prevention specialists, as well as populations at risk who will be integrally involved in the development of vaccine candidates and clinical vaccine and prevention trials. International and domestic sites are being developed, including a cadre of trained personnel, to conduct vaccine trials.

One of the foremost priorities for testing candidate vaccines continues to be a resolution of the crisis in the supply of monkeys available for HIV/AIDS vaccine studies. The supply of NHP, particularly rhesus macaques, for AIDS research and other areas of biomedical research remains a major problem for NIH-funded investigators. Both the supply of animals and the available space for conducting experiments that require adequately controlled biosafety housing are limiting and impeding exploration of new concepts in HIV vaccines. The NIH is working to find solutions to these obstacles.

The development of an HIV vaccine is a complex research challenge because HIV is unusually well equipped to elude immune defenses, as exemplified by its ability to vary extensively, to persist in viral reservoirs, and to eventually overcome the immune system. Many different vaccine approaches are being pursued. Initial studies are leading to more advanced vaccine candidates that may provide better protection. The NIH has now conducted more than 50 Phase I and 2 Phase II clinical trials of more than 30 vaccine candidates, individually or in combination, in human volunteers in collaboration with academic investigators and industry cosponsorship.

BEHAVIORAL AND SOCIAL SCIENCE

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Develop and test the predictive utility of comprehensive models for risk of HIV transmission and acquisition that reflect the complex, multidetermined nature of sexual behavior and the influences that factors distal from the immediate risk behavior have on HIV transmission and acquisition.**
- **Elucidate new and changing patterns, contexts, and kinds of drug and alcohol use and their implications for HIV transmission and acquisition, either directly or as mediators of sexual behavior.**
- **Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with sexual behavior, using methods that recognize the contributions and interactions of individual, dyadic, group, community, and societal level (structural) variables, as well as the role of the environment and behavioral implications of technological advances in medicine (e.g., rapid HIV testing, medications to treat sexual dysfunction) and changes in medical practice (e.g., simplified dosing regimens, routine and universal testing).**
- **Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with drug and alcohol use, using methods that recognize the contributions and interactions of individual, dyadic, group, community, and societal level variables, as well as the role of the environment and behavioral implications of technological advances in medicine (e.g., partial opiate agonist therapy) and changes in medical practice (e.g., directly observed therapy's integration with drug abuse treatment, increased attention to unique needs of women and ethnic/racial minorities).**
- **Support research on the interactions among factors that contribute to the cooccurrence of HIV/AIDS and other medical disorders (e.g., infectious diseases, substance abuse) and social problems (e.g., homelessness), and develop interventions to address the cooccurring conditions.**
- **Improve understanding of means to rectify disparities in consequences of and care for HIV infection through addressing the needs of various population subgroups and the stigma associated with HIV/AIDS, and through fostering integration of prevention and care services appropriate to both HIV-seropositive and HIV-seronegative persons.**

- **Test, refine, and apply findings from areas of research that are potentially relevant to HIV/AIDS issues, such as operations research, investigations of psychotherapy and behavior change with other medical conditions, management studies, family planning and reproductive health, behavioral economics, and others, to determine the applicability of principles and procedures from those research areas and disciplines to HIV/AIDS.**

The NIH supports research to further our understanding of how to change the behaviors that lead to HIV transmission—including preventing their initiation—and how to maintain protective behaviors once they are adopted in all populations at risk. The NIH sponsors research related to: developing, implementing, and evaluating behavioral and social interventions to reduce HIV transmission in a range of populations and settings; strengthening our understanding of the determinants, trends, and processes of HIV-related risk behaviors and the consequences of HIV infection; developing and evaluating behavioral strategies for preventing or ameliorating the negative physical, psychological, and social consequences of HIV infection; and improving the research methodologies employed in behavioral and social science research. A better understanding of social and cultural factors associated with HIV risk or protection, particularly in minority communities, will contribute to the successful implementation of a broader range of preventive or therapeutic measures. Drug users and their sex partners are the fastest growing segment of AIDS cases in the United States and in many other countries. Priority is being given to research that bridges and builds upon studies of the phenomenon of addiction itself, the complex interaction of alcohol use, drug use, and poor impulse control, and to developing effective HIV-related interventions from that knowledge base.

The development of new and more effective anti-HIV drugs and drug combinations has raised a host of behavioral issues. Lack of complete adherence to drug regimens may result in the development of drug-resistant strains of HIV, which could have devastating public health implications. In addition, HIV-infected individuals taking ART who experience improved health and a decline in detectable virus may believe that they are less infectious and may lapse into unsafe sexual and drug-using behaviors. This could have the effect of increasing HIV transmission, if the virus is still viable at undetectable levels. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

MICROBICIDES

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Foster the development of microbicides consisting of exogenous and endogenous agents and based on specific biological and physiological pathways involving HIV transmission across the epithelia.**
- **Identify and standardize relevant, practical, and accessible methodologies to assess preclinical/clinical safety and activity of microbicides.**
- **Foster the development of combination approaches, such as chemical and physical barriers, and of microbicides containing multiple active compounds with different chemical classes, specificities, and mechanisms of action in acceptable formulations to prevent transmission and acquisition of HIV and other sexually transmitted infections (STIs).**
- **Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from multiple scientific disciplines.**
- **Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicides clinical trials.**
- **Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, user acceptability, sexual behaviors, and the identification and development of reliable and valid behavioral tools and measurement techniques for use in trials.**
- **Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.**

The vulnerability of women to acquiring HIV infection requires the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. The NIH supports a comprehensive research program that includes the screening, discovery, development, preclinical *in vitro* and *in vivo* testing, and clinical evaluation of compounds with the potential to act as antimicrobial agents with both spermicidal and nonspermicidal activity. The NIH closely collaborates with academia and industry to identify and explore new and existing compounds as potential topical microbicidal agents.

Animal model testing and toxicity studies of potential candidate compounds are conducted through NIH-sponsored contracts before these agents are

considered for clinical trials. The NIH also supports Phase I, II, and III clinical trials of various topical microbicides, as well as behavioral and social research on the acceptability and use of microbicides among different populations. Important areas of research include the establishment of clinical trial sites and the necessary infrastructure to conduct those trials, especially in developing countries; the development of criteria for selecting potential products to be evaluated in clinical trials and for advancing them through the different phases of clinical studies; and research on ethical and behavioral issues that have an impact on clinical trials.

HIV PREVENTION RESEARCH

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Examine the ways in which social, economic, cultural, and environmental conditions, including stigma and discrimination, contribute to, or create sources of, HIV-related risk, and develop interventions based on this understanding.**
- **Examine factors associated with the initiation and sustainability of HIV prevention efforts among individuals and communities over time, as well as underlying problems (e.g., depression, substance abuse) that may impede the adoption of consistent HIV risk-reduction practices, and develop innovative strategies to address them.**
- **Elucidate the prevention-treatment interface, including the effects of HIV/AIDS treatment availability, delivery, success, and failure on HIV transmission and acquisition, and the integration of prevention into clinical care.**
- **Further explore, develop, and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of multidisciplinary HIV preventive interventions when RCTs are inappropriate or impossible to conduct, and develop guidelines to inform the field about when such non-RCT methods are appropriate to employ.**
- **In collaboration with other governmental and nongovernmental organizations, enhance support for operations, health services, and evaluation research on the design, adaptation, testing, and implementation of evidence-based HIV prevention strategies, and assess the impact of such strategies on risk behaviors at the population level.**

The NIH supports a comprehensive prevention science research agenda that targets interventions to both infected and uninfected at-risk individuals to reduce HIV transmission. Biomedical prevention research priorities include the development of topical microbicides, strategies to prevent MTCT (including a better understanding of HIV risk associated with breastfeeding), and management of STDs. NIH behavioral research strategies include interventions related to drug and alcohol use and risky sexual behaviors. Research efforts continue to identify the most appropriate intervention strategies for different populations and subepidemics in the United States and around the world.

These HIV prevention research activities include both basic and intervention studies. Research that elucidates the fundamental mechanisms

of human behavior and disease transmission and progression provides the essential basic knowledge needed for the development of testable interventions. Studies examine the range and interaction of biological, neurological, psychological, familial, social network, and other environmental factors that have an impact on HIV transmission, acquisition, or protection. While the focus of the NIH HIV prevention research program is on primary prevention of new HIV infections, it also addresses secondary prevention, that is, prevention of the negative physiological, psychological, and social consequences of disease among individuals already infected with HIV and their families, networks, and communities. This includes identifying potential cofactors, correlates, and mediators of disease progression, and developing biomedical and/or psychosocial interventions to address them.

RACIAL AND ETHNIC MINORITIES

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Enhance the capacity of minority investigators, minority institutions, and minority community-based organizations to conduct multidisciplinary HIV research.**
- **Identify biomedical, sociocultural, and structural determinants, pathways, and mechanisms that maintain or perpetuate health disparities.**
- **Develop and test innovative models, research methods, and measures of risk behavior in racial and ethnic minority areas.**
- **Further exploration of the natural history of HIV disease and its consequences for racial and ethnic minority communities.**
- **Clinical research must include racial and ethnic minorities in numbers that reflect their representation in the HIV epidemic.**

HIV infection, like many other disease states, reflects the ongoing health disparity among racial and ethnic minority communities. Prevalence of HIV infection in racial and ethnic minority communities is disproportionately higher than in majority communities. In many U.S. urban centers, the prevalence of HIV infection mimics rates found in the developing world. These findings, along with the resurgence of STDs and associated high-risk behaviors, demonstrate the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations, and improve treatment options and treatment outcomes.

OAR is directing increased resources toward research to develop new interventions that will have the greatest impact on these groups. These include interventions that address the cooccurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. The NIH is making significant investments to improve research infrastructure and training opportunities for minorities and will continue to ensure the participation of minorities in AIDS clinical trials, as well as in natural history, epidemiologic, and prevention studies. OAR has provided additional funds to projects aimed at increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors, and HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding the portfolio of population-based research. One of these

projects is a series of Training and Career Development Workshops for racial and ethnic minority investigators. These workshops provide minority investigators with an opportunity to learn more about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

The NIH supports a broad array of behavioral intervention studies with specific focus on African American populations. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences of multiple coinfections, effectiveness of therapeutic regimens, and the impact of health care access and adherence to therapeutic regimens on disease outcomes. The increasing number of minority AIDS cases underscores the importance of research to define and utilize cultural, social, and contextual factors that affect HIV risk behaviors. The role of alcohol and drug use in facilitating HIV transmission through social networks in all communities also is being explored within these social frameworks.

WOMEN AND GIRLS

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Study the biology of the reproductive tract and rectum of HIV-infected and HIV-uninfected women and girls, integrating studies of physiology, immunology, microbiology, and anatomy.**
- **Elucidate a range of host-virus interactions through the course of HIV infection (in particular, during primary HIV infection) and across the life cycle in women and girls.**
- **Develop and continue existing clinical studies—including biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social—to ascertain the effects of sex and gender in HIV infection among women and girls, and ensure dissemination of resulting information.**
- **Enhance basic behavioral and social research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences—including gender-based stigma and discrimination, and integrate this work into the design and evaluation of HIV prevention and care interventions.**
- **Explore factors that influence development, adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition, and ensure dissemination of resulting information.**
- **Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.**

Women experience HIV/AIDS differently from men both physiologically and socially. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than do men. This finding may have implications for care and treatment of HIV-infected women, particularly with ART. Women's childbearing capacity also differentiates their HIV/AIDS experiences from men's, as HIV-infected pregnant women may transmit the virus to their fetuses and infants. Women in most societies are the primary care providers for children and older people, so their early deaths from AIDS and its complications often leave dependents with no one to care for them. NIH researchers are studying the ways in which sex and gender confer vulnerability to, or protection from, HIV infection and AIDS among women and girls—in general, and relative to men—in diverse geographical settings and during

different stages of the life course. There are many research questions that remain unanswered about specific anatomical and physiological characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection. Studies will focus on factors in HIV acquisition, including the influence of hormonal modulation on viral replication and immune responses in the reproductive tract, and cofactors, such as coincident infections with other STD pathogens.

INTERNATIONAL RESEARCH

RESEARCH PRIORITIES OF THE FY 2006 PLAN

- **Develop in-country HIV/AIDS research and training infrastructure for the conduct of integrated prevention and treatment or care intervention research, integrating new activities into existing health care and prevention services.**
- **Define the spectrum of HIV-related disease and its response to treatment as it applies to diverse geographic settings, and develop effective prevention and treatment interventions to limit the impact of HIV-related disease.**
- **Conduct studies (experimental and observational) to identify the appropriate modalities of introduction and long-term use of ART in resource-limited settings.**
- **Support studies to identify effective, appropriate, and sustainable interventions to curtail HIV transmission. Such interventions should encompass the prevention of all transmission modalities (e.g., heterosexual, mother-to-child, transmission related to drug and alcohol use) and their mutual interaction. Intervention modalities to decrease HIV transmission should integrate evidence acquired from biomedical, behavioral, and other research areas and should identify and target all at-risk populations.**
- **Study and address barriers to the conduct of international research, including access to health and research facilities for at-risk populations, research regulatory requirements, consistent application of bioethics principles, institutional factors (e.g., availability of expert peer review groups and program personnel), and others.**

The Joint United Nations Programme on HIV/AIDS (UNAIDS) report *AIDS Epidemic Update: December 2001* states that “AIDS has become the most devastating disease humankind has ever faced.” HIV/AIDS is the fourth largest killer worldwide; in sub-Saharan Africa, it is the leading cause of death. The impact of AIDS on the developing nations of Africa, Asia, Europe, and Latin America is staggering, with even greater potential disaster to come. The cost in lost productivity and profitability, sickness and death, and a significant reduction in the skilled workforce in developing countries will have major economic impact for the United States and for the economy and security of the world.

Since the early days of the epidemic, the NIH has supported research efforts in countries affected by HIV and AIDS. Beginning in 1984 with a research

project in Haiti and the establishment of Projet SIDA in 1985 in what was then Zaire, the NIH has maintained a strong international research portfolio. The NIH has expanded its research effort to encompass approximately 85 countries around the world. Results of this research benefit not only the people in countries where the research is conducted, but people affected by HIV/AIDS worldwide. NIH international research includes efforts to develop: HIV vaccine candidates and chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and nondrug strategies to prevent MTCT; therapeutics for HIV-related coinfections and other conditions; and approaches to using ART in resource-poor settings.

Before prevention and treatment interventions can be implemented in different geographic settings, their safety must be confirmed and efficacy demonstrated in such settings through clinical trials and other intervention research. To develop vaccines and other prevention strategies that will be effective globally, Phase I safety studies are first conducted in small populations in the United States. To establish efficacy, large numbers of at-risk study participants are necessary. Around the world, the predominant mode of HIV transmission is heterosexual. Among heterosexuals in the United States, the rate of HIV infection is estimated to be approximately 1.5 percent. In some developing countries, the rate of heterosexual HIV infection is 13–25 percent. Because of the large populations at high risk of infection, prevention studies can be more efficiently conducted in those settings.

Although industrialized nations have experienced a dramatic decrease in transmission of HIV from infected mother to her child, preventing this transmission is a significant challenge in resource-poor settings of the world; strategies that can effectively be used in such settings continue to be pursued. Research also is needed to devise strategies to decrease transmission in medical settings.

Development of a research infrastructure is essential to these research programs. Specific international infrastructure needs include: (1) developing research sites through establishment of stable, targeted cohorts, development of recruitment strategies, and enhancement of laboratory, clinical, and data management capabilities; (2) increasing the number of scientists, clinicians, and health care workers trained in basic, clinical, and behavioral research, data management, and ethical considerations; (3) developing research collaborations; and (4) transferring appropriate clinical and laboratory technologies.

Training, Infrastructure, and Capacity Building

The NIH will continue to support training of domestic and international biomedical and behavioral AIDS researchers, as well as the improvement of facilities and equipment for the conduct of AIDS-related research, including facilities for animal model research. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from minority communities into research careers and to build research infrastructure in minority institutions. The NIH Loan Repayment Program was mandated by Congress under Public Law 100-607 in 1988 and authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at the NIH. The NIH also sponsors programs to train scientists in developing countries to undertake AIDS research. The National Primate Research Centers program provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of NHP species to support diverse requirements for AIDS-related research.

Information Dissemination

Effective information dissemination approaches will continue to be integral to HIV prevention and treatment efforts. Such programs are critical in light of the continuing advent of new and complex ARV treatment regimens, the adherence issues related to HIV/AIDS treatment, the need for research communities to work and communicate globally, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of HIV infections in specific population groups, such as minorities and women, also underscore the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

AIDS Research Benefits Other Research

AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. AIDS research has provided an entirely new paradigm for drug design, development, and clinical trials to treat viral infections. For example, the drug known as 3TC, developed to treat HIV/AIDS, is now the most effective therapy for chronic HBV infection. Drugs developed to prevent and treat

AIDS-associated OIs also provide benefit to patients undergoing cancer chemotherapy or receiving anti-transplant-rejection therapy. AIDS research also is providing a new understanding of the relationship between viruses and cancer.

APPENDIX A:

Summary of
HIV/AIDS Funding

HIV/AIDS FUNDING BY NIH INSTITUTE, CENTER, AND OFFICE

| Institute/Center | FY 2003 Actual | FY 2004 Conference | FY 2005 Estimate |
|-------------------------|---------------------------|-------------------------------|-----------------------------|
| NIAID | \$1,309,831 | \$1,396,836 | \$1,457,464 |
| NIDA | 301,514 | 312,979 | 315,732 |
| NCI | 263,285 | 267,857 | 268,126 |
| NIMH | 174,851 | 181,219 | 184,111 |
| NCRR | 145,965 | 152,544 | 158,126 |
| NICHD | 125,166 | 130,311 | 134,064 |
| NHLBI | 74,890 | 75,074 | 75,292 |
| NIGMS | 52,044 | 54,570 | 55,073 |
| NINDS | 45,266 | 47,155 | 47,754 |
| NIDDK | 29,515 | 30,828 | 31,403 |
| NIAAA | 25,718 | 26,784 | 27,391 |
| NIDCR | 25,068 | 25,192 | 25,192 |
| FIC | 21,371 | 22,603 | 23,170 |
| NEI | 12,694 | 12,663 | 12,663 |
| NINR | 11,800 | 12,083 | 12,336 |
| NIEHS | 8,533 | 8,717 | 8,772 |
| NLM | 7,130 | 7,416 | 7,516 |
| NIAMS | 6,578 | 6,719 | 6,753 |
| NHGRI | 6,698 | 6,877 | 6,917 |
| NIA | 5,344 | 5,489 | 5,503 |
| NCCAM | 2,700 | 2,800 | 2,800 |
| NIDCD | 1,727 | 1,748 | 1,748 |
| NIBIB | 966 | 1,056 | 1,056 |
| SUBTOTAL | 2,658,654 | 2,789,520 | 2,868,962 |
| OD | 57,564 | 60,432 | 61,435 |
| TOTAL | \$2,716,218 | \$2,849,952 | \$2,930,397 |

APPENDIX B:

Office of AIDS Research
Advisory Council

OFFICE OF AIDS RESEARCH ADVISORY COUNCIL

Interim Chairperson

Gina M. Brown, M.D.

Assistant Professor

Department of Obstetrics/Gynecology

Women's Medical Director

Columbia University College of Physicians
and Surgeons

Medical Director

Cicatelli Associates, Inc.

Executive Secretary

Jack Whitescarver, Ph.D.

Director

Office of AIDS Research

Office of the Director, NIH

U.S. Department of Health and
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Members

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Care Center for Women at Shands

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Lawrence O. Gostin, LL.D., J.D.

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Georgetown University Law Center

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Senior Research Scientist

Harvard Center for Population and
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Judith A. Levy, Ph.D.

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School of Public Health

University of Illinois at Chicago

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Former CEO and President

Ingenix Pharmaceutical Services

C. Randal Mills, Ph.D.

Vice President, Operations

Regeneration Technologies, Inc.

Julie Overbaugh, Ph.D.

Division of Human Biology

Fred Hutchinson Cancer Research Center

Robert R. Redfield, M.D.

Director of Clinical Care and Research

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Mr. Steven F. Wakefield

Associate Director for Community Relations
and Education
HIV Vaccine Trials Network
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National Advisory Council on Drug Abuse

David H. Vlahov, Ph.D.

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Center for Urban Epidemiologic Studies

New York Academy of Medicine

National Advisory Mental Health Council

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Osher Foundation Distinguished Professor
in Integrative Medicine

Director, Osher Center for

Integrative Medicine

University of California, San Francisco

APPENDIX C:

**FY 2006 Plan and
Budget Timeline**

OAR ANNUAL PLAN AND BUDGET PROCESS FY 2006 Timeline

| PLAN | |
|----------------------|------------------------------------------------------------------------------------------------|
| February 2004 | Draft 1 External Consultants NIH Program Staff IC AIDS Coordinators IC Directors |
| April 2004 | Draft 2 OAR Advisory Council Comments |
| August 2004 | Final Plan Published |
| BUDGET | |
| May 2004 | ICs Prepare Budget Using Draft Plan |
| June 2004 | Draft Budget Developed Based on IC Request |
| August 2004 | AIDS Budget Submitted to Director, NIH |
| August–December 2004 | NIH Budget to Secretary, DHHS DHHS Budget to OMB |
| February 2005 | FY 2006 President’s Budget to Congress |
| March 2005 | Appropriations Subcommittee Hearings |
| April–September 2005 | House, Senate, Conference Action |
| October 2005 | FY 2006 Begins |

